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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/910,461	07/20/2001	Peter D. Gluckman	37522-1002C1	2772

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FLIESLER DUBB MEYER & LOVEJOY, LLP
FOUR EMBARCADERO CENTER
SUITE 400
SAN FRANCISCO, CA 94111

EXAMINER	
CELSA, BENNETT M	
ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 04/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

File copy

Office Action Summary

Application No.	Applicant(s)
09/910,461	Gluckman et al.
Examiner	**Art Unit**
Bennett Celsa	1639

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *11-46* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *11-46* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *4-6*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of the Claims

Claims 11-46 are currently pending and under consideration to the extent of the elected invention (e.g. GLY-PRO-GLU)..

Election/Restriction

1. Applicant's election without traverse of GLY-PRO-GLU in Paper No. 10 is acknowledged.

Claim Objections

2. Claim 36 is objected to because of the following informalities: the term "introvenous" is misspelled.. Appropriate correction is required.

Claim Rejections - 35 USC § 112

3.The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 38-41 and 43-44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 38-41 and 43-44, the terms "said neural damage" and "said ischemic neural damage" lack clear antecedent basis.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in-
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
> (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was

made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 11-16, 24-27, 30-31 and 36-46 are rejected under 35 U.S.C. 102(b) as anticipated by or in the alternative obvious over Sara EP0366638 (5/90) alone and further in view of the specification pages 1-2 to demonstrate inherency e.g. damage/loss of glial cells resulting from due to neural damage/injury e.g. from asphyxia/ischemia/hypoxia/stroke; and dementia disorders such as Alzheimer's addressing non-dopaminergic neurons.

The presently claimed invention is directed to a method for "protecting" (e.g. preventing) neural cell death resulting from injury or disease by administering Gly-Pro-Glu, Gly-Pro, or Pro-Glu in a "neuroprotective amount" to a mammal.

Sara discloses the administration of dipeptides (e.g. preferably gly-pro and pro-glu) and most preferably the tripeptide gly-pro-glu in pharmaceutical formulations to mammals in order to promote neuromodulation (see e.g. col. 1 lines 1-34) to treat neurodegenerative diseases and neural injury; such disease including (but not limited to) Alzheimers and neurological disorders dealing with non-dopaminergic neurons; in addition to neurotransmitter diseases (e.g. see col. 1, lines 28- top of col. 2)., and such injuries/damage including anoxic and ischemic brain damage (e.g. stroke and asphyxia); thus teaching the "the treatment of neural damage" (E.g. claim , Thus, the reference treatment of neurodenerative/neurocatabolic disease states and ischemic brain

damage (e.g. stroke and asphyxia) addresses the treatment of injuries or disease which result in neural cell death.

The administration of the Sara peptides is via any "suitable route of administration"; including administration directly into the spinal fluid or systemic administration (e.g. oral or nasal). The reference further teaches systemic administration, including oral and nasal; as well as subcutaneous, intramuscular or intravenous. The reference teaching of systemic administration, including oral and nasal, would lead the skilled artisan to immediately envisage (e.g. anticipate) the small number of other conventional systemic administration routes (e.g. rectal, subcutaneous, inhalation, intraperitoneal or intramuscular), or alternatively, these systemic administration routes would have been prima facie obvious to one of ordinary skill in the art at the time of applicant's invention. The administration of the Sara peptides prior to an event "considered likely to lead to injury to glial cells or non-dopaminergic neural cells " would be immediately envisaged (e.g. anticipated) or in the alternative obvious to one of ordinary skill in the art since the reference teaching of the ability of the Sara peptides to treat "neural injury or disease states" within the scope of the presently claimed invention (e.g. asphyxia, ischemia, stroke) would envisage the use of such peptides prior to the onset of symptoms if foresees the likelihood of nerve damage resulting from a given activity.

The reference teaching of treating disease states would immediately envisage (e.g. anticipate) treatment within a reasonable time subsequent to the appearance of symptoms (e.g. up to 100 hours after CNS insult, and preferably 0.5 to 8 hours) or in the alternative, it would have

been prima facie obvious to the skilled artisan to administer the reference peptide within a reasonable time following the onset of disease symptoms in order to effectively treat the disease, which would encompass up to 100 hours, and preferably 0.5 to 8 hours after disease onset.

The Sara reference teaching of the administration of "small quantities" of peptide "as low as fractions of milligrams" would anticipate the broad range of claim 55 or alternatively it would be obvious to determine an optimum range which would fall within the presently claimed broad range since the reference further motivates the skilled artisan to adjust the dosage using conventional means to achieve an optimum quantity (e.g. nanograms reaching the target site) which would be reasonably expected to result in a concentration that would fall within the broad claimed range (see e.g col. 2, lines . 45-55).

The prior art method must inherently "prevent" neural cell death" via the same mechanism (e.g. meet mechanism limitation of present claim 56) because the reference teaches the administration of the *same peptide(s)* to the same host(s) in the *same amount (s) to treat the same diseases and/or neural injuries affecting the same neurons(glial cells/non-dopaminerci)* *See In re Best*, 195 USPQ 430,433 (CCPA 1977); *Ex parte Novitski*, 26 USPQ2d 1389 (B.P.A.I, 1993).

8. Claims 11-17, 24-27, 30-31 and 36-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sara EP0366638 (5/90) alone (and further in view of the specification pages 1-2 to demonstrate inherency e.g. damage/loss of glial cells resulting from due to neural damage/injury e.g. from asphyxia/ischemia/hypoxia/stroke; and dementia disorders such as Alzheimer's addressing non-dopaminergic neurons) as applied to claims 11-16, 24-27, 30-31 and 36-46 above, and further in view of Sibalis US Pat. No. 5,032,109 (7/1991).

As discussed in the above anticipation/obvious rejection, hereby incorporated by reference in its entirety, Sara discloses the use of dipeptides (e.g. preferably gly-pro and pro-glu) and most preferably the tripeptide gly-pro-glu in pharmaceutical formulations for administration to mammals in the CNS and PNS to all neural tissue , cells or tissue of neural origin (e.g. see col. 2, lines 8-15) in the treatment of neurodegenerative and catabolic neuronal disease states including ischemia, Alzheimer's etc.

The Sara reference, although teaching "any suitable route" of administration including "subcutaneous, intramuscular or intravenous administration" (e.g. see Sara col. 2, especially lines 35-45), differs from the presently claimed invention (E.g. claim 17) by failing to explicitly disclose "applying an electrophoretic procedure in aid of said administration of GPE".

However, the Sibalis reference patent teaches the benefits of transdermal delivery of "polypeptides containing about three to 20 alphaamino acid units" (which would include GPE) using electrophoresis including "minimal patient discomfort"; "without irritation or reddening of

the skin and without tingling or other sensations" all discomforts of which may be present via administration by other routes (e.g. injection).

Accordingly, one of ordinary skill in the art would have been motivated to utilize transdermal administration of small peptides such as Sarah's GPE via electrophoresis in order to minimize patient discomforts realized using other modes of administration.

Thus, it would have been obvious to one of ordinary skill in the art at the time of applicant's invention to apply an electrophoretic procedure as an aid in administering GPE in the Sarah method in order to obtain the benefits therefrom (e.g avoid discomforts inherent in other modes of administration e.g. injection with tingling, skin reddening or irritation; sight of the needle).

9. Claims 11-16 and 18-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sara, EP0366638 (5/90) alone (and in view of specification pages 1-2 to demonstrate inherency e.g. damage/loss of glial cells due to neural damage/injury e.g. from asphyxia/ischemia/ hypoxia/stroke; and dementia disorders such as Alzheimer's addressing non-dopaminergic neurons) as applied to claims 11-16, 24-27, 30-31 and further in view of Gluckman et al., WO93/02695 (2/93).

As discussed in the above anticipation/obvious rejection, hereby incorporated by reference in its entirety, Sara discloses the use of dipeptides (e.g. preferably gly-pro and pro-glu) and most preferably the tripeptide gly-pro-glu in pharmaceutical formulations for administration to

mammals in the CNS and PNS to all neural tissue , cells or tissue of neural origin (e.g. see col. 2, lines 8-15) in the treatment of neurodegenerative and catabolic neuronal disease states including ischemia, Altzheimer's etc.

However, the Sara reference fails to explicitly disclose:

a. the administration of the Sara peptides prior to elective procedures (e.g. cardiac bypass surgeries/brain surgeries; and via "maternal circulation" during parturition) (e.g. present claims 18 and 20-23).

b. treatment within a reasonable time subsequent to the appearance of symptoms (e.g. up to 100 hours after CNS insult, and preferably 0.5 to 8 hours) utilizing an effective amount of peptide (e.g. ; 0.1 to 1000ug per 100 gm of body weight) (claims 28-29);

c. the different types of "direct" spinal fluid administration (e.g. cerebro-ventricular injection, injection into the cerebral parenchyma or lateral cerebro ventricle shunt) (e.g. present claims 32 and 33);

d. the administration of GPE "in combination with artificial cerebrospinal fluid" (e.g. present claims 34-35).

Gluckman et al., teaches a method for the treatment or prevention of CNS damage caused by neurodegenerative disease and trauma which primarily causes damage to glia and/or other non-cholinergic cells of the CNS (e.g. See abstract; pages 1-3 and claims 1-15). For example, Gluckman et. suggest that it is desirable to prevent or reduce the amount of CNS damage which may be suffered as a result of induced cerebral asphyxia during elective surgeries e.g. as occurs

during cardiac bypass surgery and child birth (e.g. "perinatal asphyxia") (see bottom of page 1 to top of page 2). The Gluckman peptide medicament(s) can be administered up to 100 hours after CNS insult, and preferably 0.5 to 8 hours after CNS insult via surgical shunt into the cerebro ventricle in amounts of 0.1 to 1000ug per 100 gm of body weight (e.g. see pages 3-4). The Gluckman peptides can be administered via "direct" spinal fluid administration (e.g. cerebro-ventricular injection, injection into the cerebral parenchyma or lateral cerebro ventricle shunt) (e.g. see pages 3-4 and 6) or optionally "in combination with artificial cerebrospinal fluid" (e.g. page 10, lines 8-15). The Gluckman administered peptide preferably comprises IGF-1 and/or analogues thereof including synthetic analogues of IGF-1 (e.g. see claims 1 and 13). It is noteworthy that the Gly-Pro-Glu peptide, as presently claimed, is derived from the N-terminal three amino acids of IGF-1 peptide..

Thus, the Gluckman reference provides conventional amounts and means of directly administering (e.g. maternal circulation when addressing fetal distress) peptides for use in treating neurodegenerative disease, trauma and their sequelae (e.g. neural death or damage) including the desirability to prevent or reduce the amount of CNS damage which may be suffered as a result of induced cerebral asphyxia during elective surgeries e.g. as occurs during cardiac bypass surgery and child birth (e.g. "perinatal asphyxia") (see bottom of page 1 to top of page 2). .

Accordingly, one of ordinary skill in the art would be motivated to employ the same means and amounts of administration as Gluckman when employing analogous peptides for treating the same diseases and states as addressed by the Gluckman reference.

Thus, it would have been prima facie obvious to the skilled artisan at the time of applicants' invention to prevent/treat neural cell death during elective procedures (e.g. cardiac bypass surgeries; brain surgeries, cord occlusion) likely to result in loss of neurons (e.g. cell death; including glial cells) by administering Gly-pro-glu as taught by Gluckman.

Similarly, it would have been prima facie obvious to the skilled artisan to select a specific direct method of CSF administration (e.g. cerebroventricular injection) as taught by Gluckman for administration of the Gly-Pro-Glu Sara peptide; and further administer the therapeutic peptide with artificial CSF as taught by Gluckman.

Additionally it would have been prima facie obvious to the skilled artisan to administer the Sara peptide upon a reasonable time following CNS symptoms (e.g. up to 100 hours, preferably 0.5 to 8 hours) in effective amounts (e.g. 0.1 to 1000ug per 100 gm of body weight) as taught by Gluckman.

General information regarding further correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Celsa whose telephone number is (703) 305-7556.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew J. Wang (art unit 1639), can be reached at (703)306-3217.

Any inquiry of a general nature, or relating to the status of this application, should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Bennett Celsa (art unit 1639)
April 14, 2003

BENNETT CELSA
PRIMARY EXAMINER